S162

2-hour Symposium

Challenges in the clinical development of new antibacterial agents

Development of drugs for treatment of abdominal infections caused by multidrug-resistant pathogens

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Intra-abdominal infections are composed of two different entities: community-acquired infections (CAI) and heath-care associated infections (HCAI). CAI and HCAI are opposite in their frequency, the ease of the diagnosis, the delay of surgical management and their aetiologies. They share some similarities such as their polymicrobial nature involving aerobes (Gram-positive and Gram-negative bacteria) and anaerobes.
In terms of multidrug resistant strains, a discrepancy between CAI and HCAI is mainly reported in western countries with high proportions of MDR strains in HCAI and lower proportions in CAI. The data available, although limited, suggest that in the rest of the world, especially in Asia, high proportions of multi-drug resistant (MDR) bacteria are reported in both conditions. These difficult-to-treat micro-organisms are mainly represented by Enterobacteriaceae while non-fermenting Gram-negative aerobes are reported in second line infections. The second source of concern is related to enterococci (vancomycin-resistant and/or penicillin resistant strains) for Gram-positive organisms, especially in HCAI. Until recently, the guidelines have rarely recommended to target MDR bacteria at the empirical phase of treatment for CAI. However on the basis of epidemiological analyses, the rapidly moving situation leads to consider these MDR in many countries.
The therapeutic rules for intra-abdominal infections are based on adequate source control and antibiotic therapy targeting Enterobacteriaceae and anaerobes. The need to treat enterococci remains a source of debate in CAI but is commonly admitted in HCAI. The debate on the need to treat all the organisms or only the most relevant ones is blurred by the absence of clear knowledge of the pathogenicity of most bacteria cultured in surgical samples and the absence of relevant biomarkers or surrogates.
Based on this duality between CAI and HCAI, the development of new drugs for intra-abdominal infections raises some specific issues. How selecting the cases? Is it relevant to include low severity cases such as complicated appendicitis in the evaluation of these new compounds? What should be exclusion criteria? How to take into account the severity of the cases? How to assess adequacy of source control? What should be the comparator drug in the clinical trials? What countries should be involved in the evaluation of these new drugs? How to assess clinical response? What should be the duration of antibiotic therapy? Do we need an oral switch during the evaluation process? These issues remain debated and the evaluation of new drugs is for the moment still based on "conventional rules". In the near future, different approaches could be proposed to answer more rapidly to the threats of emerging MDR bacteria.